

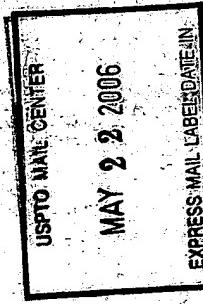
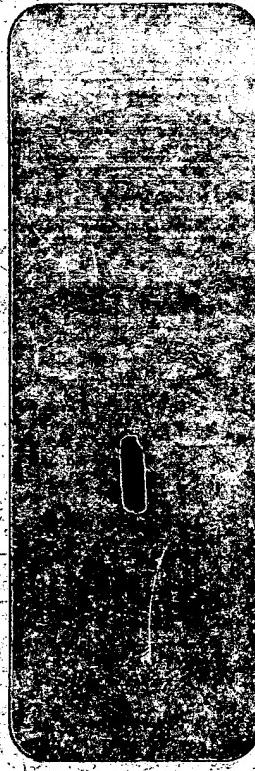
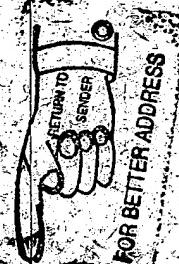
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,336	08/22/2003	Kathryn E. Uhrich	1435.021US2	8315
21186	7590	05/05/2006	EXAMINER	
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A. P.O. BOX 2938 MINNEAPOLIS, MN 55402			FUBARA, BLESSING M	
		ART UNIT	PAPER NUMBER	
			1618	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,336	UHRICH, KATHRYN E.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 30 January 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-11, 13, 18, 21-26 and 35-40 is/are pending in the application.
 - 4a) Of the above claim(s) 6 and 9-11 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-5, 7, 13, 18, 21-26 and 35-40 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>4/24/06</u> |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/31/05</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Examiner acknowledges receipt of response to pre-exam formalities filed 11/15/2004; IDS filed 1/31/05, power of attorney filed 03/24/06 and response to election requirement filed 1/30/06.

Election Requirement

Applicant has canceled claims 12, 14-17, 19, 20 and 27-34 in response to the election requirement mailed 07/28/05, applicant has also amended claims 1, 2, 4, 13, 18, 21, 23 and 24; and applicant has further added new claims 35-40. Therefore, claims 1-11, 13, 18, 21-26 and 35-40 are pending.

Applicants elected mycophenolic acid (MPA), ester linkage in the response filed 1/30/06 in response to the election requirement. Furthermore, in telephone interview on 4/24/04 with attorney Robert Harris, applicant elected C-14 hydrocarbon chain for R². Applicant identifies claims 1-4, 7, 8, 13, 18, 21-26 and 35-40 as reading on the elected species. The search is extended to include penicillin and melphalan. Therefore, claims 1-5, 7, 8, 13, 18, 21-26 and 35-40 are examined. Claims 6 and 9-11 are withdrawn from consideration as non-elected claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that application was in possession of the claimed invention. The specification does not describe all polyanhydride molecules having good number of the biologically active compounds listed in claims 4 and 5 as part of the backbone of the polyanhydride.

Claims employing these biologically active agents are not fully described in the specification; cephalexin, amoxicillin, carbidopa, levodopa and amtenac are exemplified. Thus, the specification does not inform the public of the limits of the monopoly asserted. The list of biologically active agents provided in the specification in paragraphs [0034], [0035], [0036], [0037] and [0050] of the published application represents only an invitation to experiment regarding all the possible biologically active agents claimed in the instant application that can be delivered by degradation/break down/hydrolysis of the polyanhydride molecule that they are part of.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-5, 7, 13, 18, 21-26 and 35-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Uhrich (WO 99/12990).

The WO publication discloses polyanhydride for delivery of therapeutic salicylates (page 9, lines 22-33), antiulcerative rosaproston, vasoconstricting drug midocrine and phenylethanolamines (page 10, lines 8-15), acyclovir, melphalan, penicillin (page 11, lines 25-36). Claims 35-40 represent the intended uses of the polymer composition or the structure that the formulation will be made into, and since the composition polyanhydride composition of the prior art and that of the instant claims are the same, the formulation/product/polyanhydride of the prior art can also be processed into the forms recited in the claims 35-40. The group contemplated for the linker group are ether, ester, amide, anhydride, carbonate, urethane or sulfide groups having alkylene group containing 1-20 carbon atoms or alkoxy groups having 2-20 carbon atoms (page 3, lines 2-9). While applicant elected C-14 hydrocarbon, claims 22-24 are included in this initial examination since that prior art 1-20 carbon atoms.

5. Claims 1-11, 13, 18, 21-26 and 35-40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Domb (US 5,660,851).

Domb discloses polyanhydride ocular inserts (abstract); in embodiment A, carboxylic acid containing substances are covalently attached to a polymer that contains pendant carboxylic acid groups, the attachment is through anhydride linkage and the drug is released over time by hydrolysis of the anhydride bonds (Column 4, lines 38-46); in embodiment B, the drug is dispersed within the anhydride polymer or copolymer matrix (column 4, lines 65-64); in embodiment C, carboxylic containing substance for delivery is covalently attached to pendant carboxylic acid of the polymer through methylene diester bonds which degrades in vivo over time (column 5, lines 14-16). L-dopa, carbidopa and mycophenolic acid are few of the examples of carboxylic acid drugs that can be used in embodiments A and C (column 8, lines 20-

65; column 10, lines 2-14; column 11, lines 25-57). While claims 35-40 recite the intended application of the polymer, Domb discloses that the composition are from into implantable devices, compressed tablets for oral use and for coating of tablets for oral controlled drug delivery (column 14, lines 56-64). In the alternate, it would have been obvious to use any of the drugs suggested by Domb in the polyanhydride with the expectation of having them be released over time according to Domb.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhrich (WO 99/12990).

The WO publication is described above. Instant claim 8 further limits claim 3 to bucillamine, mycophenolic acid, procodazole, romurtide and ubenimex. However, melphalan and these agents recited in claim 8 are all anticancer drugs. Therefore, one anticancer drug can be used in place of another anticancer drug. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the melphalan containing polyanhydride and to use other anticancer drugs in place of the melphalan with the expectation that the polyanhydride when it hydrolyzes or biodegrades would release the anticancer agents.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Blessing Fubara
Patent Examiner
Tech. Center 1600



Interview Summary	Application No.	Applicant(s)	
	10/646,336	UHRICH, KATHRYN E.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

All participants (applicant, applicant's representative, PTO personnel):

(1) Blessing M. Fubara (Examiner). (3) _____.

(2) Robert Harris (Attorney). (4) _____.

Date of Interview: 24 April 2006.

Type: a) Telephonic b) Video Conference
c) Personal [copy given to: 1) applicant 2) applicant's representative]

Exhibit shown or demonstration conducted: d) Yes e) No.
If Yes, brief description: _____.

Claim(s) discussed: N/A.

Identification of prior art discussed: N/A.

Agreement with respect to the claims f) was reached. g) was not reached. h) N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant's representative elected 14 carbon atom chain as R2.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(use as many sheets as necessary)

Approved for use under PTO rules 1.73 and 1.97. GPO: 2000 OMB Control No. 0651-0036.

U.S. Patent and Trademark Office

Sheet 1 of 7

Attorney Docket No: 1435.021US2

US PATENT DOCUMENTS				
Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document	Filing Date If Appropriate
bf	US-2003/0035787A1	02/20/2003	Uhrich, Kathryn E.	09/24/2002
bf	US-2004/0038948A1	02/26/2004	Uhrich, Kathryn E.	02/18/2003
bf	US-2004/0044125A1	03/04/2004	Uhrich, Kathryn E.	08/25/2003
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bf	US-5,902,110	05/11/1999	Alfano, Michael C., et al.	11/03/1997

EXAMINER

Blessing Fubara

DATE CONSIDERED

4/23/06

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
use as many sheets as necessary

[Jan 31, 2005]

<i>Complete if Known</i>	
Application Number	10/646,336
Filing Date	August 22, 2003
First Named Inventor	Uhrich, Kathryn
Group Art Unit	1615
Examiner Name	Fubara, Blessing

Attorney Docket No: 1435.021US2

Sheet 2 of 7

9F	US-5,902,599	05/11/1999	Anseth, Kristi S., et al.	02/20/1996
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Examiner Initials*	Foreign Document No	Publication Date	Name of Patentee or Applicant of cited Document	T ²
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	CA-2393676	07/06/2002	Uhrich, Kathryn , et al.	
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	WO-01/28492	04/26/2001	Uhrich, Kathryn E.	
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	WO-97/39738	10/30/1997	Ignatious, Francis , et al.	
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	WO-99/29885	06/17/1999	Koch, Rainhard , et al.	
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First Named Inventor	Uhrich, Kathryn
Group Art Unit	1615
Examiner Name	Fubara, Blessing

Sheet 3 of 7

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Sheet 4 of 7

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Sheet 6 of 7

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Sheet 7 of 7

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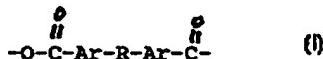
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(71) Applicant (for all designated States except US): RUTGERS, THE STATE UNIVERSITY [US/US]; Old Queens, Somerset Street, New Brunswick, NJ 08903 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): UHRICH, Kathryn [US/US]; 920 Bloomfield Street, Hoboken, NJ 07030 (US). (74) Agent: BUTCH, Peter, J., III; Synnestvedt & Lechner LLP, 2600 Aramark Tower, 1101 Market Street, Philadelphia, PA 19107-2950 (US).			

(54) Title: POLYANHYDRIDES WITH THERAPEUTICALLY USEFUL DEGRADATION PRODUCTS



(57) Abstract

An aromatic polyanhydride having a repeating unit with structure (I) wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group. Ortho-substituted bis-aromatic dicarboxylic acid anhydride monomers and ortho-substituted bis-aromatic dicarboxylic acid intermediates thereof are also disclosed, as well as implantable medical devices, such as scaffolding implants for tissue reconstruction, drug delivery systems prepared from the aromatic polyanhydrides, as well as therapeutic oral dosage forms and treatment methods.

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**POLYANHYDRIDES WITH THERAPEUTICALLY
USEFUL DEGRADATION PRODUCTS**

TECHNICAL FIELD

The present invention relates to biocompatible aromatic polyanhydrides having improved degradation properties and processability and unique therapeutic properties. In particular, the present invention relates to aromatic polyanhydrides produced from ortho-substituted bis-aromatic carboxylic acid anhydrides. The present invention also relates to ortho-substituted bis-aromatic dicarboxylic acids useful in the preparation of the aromatic polyanhydrides of the present invention.

BACKGROUND ART

Biocompatible and biodegradable aromatic polyanhydrides are disclosed by U.S. Patent Nos. 4,757,128 and 4,997,904. However, unless incorporated into a copolymer containing a more hydrophilic monomer, such as sebamic acid, the aromatic polyanhydrides of the prior art have slow degradation times as

well as relatively insoluble degradation products. A major drawback to the prior art aromatic polyanhydrides is their insolubility in most organic solvents.

5 Biocompatible and biodegradable aromatic polyanhydrides prepared from para-substituted bis-aromatic dicarboxylic acids are disclosed by U.S. Patent No. 5,264,540. The para-substitution pattern results in higher melt and glass transition temperatures and decreased solubility, thus ultimately making these para-substituted polymers difficult to process.

10 A need exists for biocompatible and biodegradable aromatic polyanhydrides having improved degradation and processing properties, as well as therapeutic utilities.

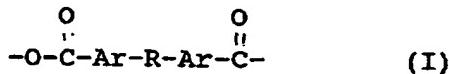
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SUMMARY OF THE INVENTION

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This need is met by the present invention. It has now been discovered that the preparation of aromatic polyanhydrides from ortho-substituted bis-aromatic carboxylic acid anhydrides disrupts the crystallinity of the resulting polymer, enhancing solubility and processability, as well as degradation properties. Therefore, according to one aspect of the present invention, an aromatic polyanhydride is provided having a repeated unit within the structure of Formula I:

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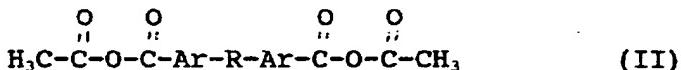


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wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group. Ar and R are preferably selected so that the hydrolysis products of the polyanhydrides have a chemical structure resembling pharmaceutically-active materials, particularly salicylates such as aspirin, non-steroidal anti-inflammatory naphthyl or phenyl propionates such as ibuprofen, ketoprofen, naproxen, and the like, or

other aromatic anti-inflammatory compounds such as indomethacin, indoprofen, and the like. In particular, Ar is preferably a phenyl group and R is preferably -Z₁-R₁-Z₁, in which R₁ is a difunctional moiety and both Z₁'s are independently either an ether, ester, amide, anhydride, carbonate, urethane or sulfide groups. R₁ is preferably an alkylene group containing from 1 to 20 carbon atoms, or a group with 2-20 carbon atoms having a structure selected from (-CH₂-CH₂-O-)_n, (-CH₂-CH₂-CH₂-O-)_n, and (-CH₂-CHCH₃-O-)_n.

Ortho-substituted bis-aromatic carboxylic acid anhydrides of the present invention are novel and non-obvious intermediate compounds having utility in the preparation of the aromatic polyanhydrides of the present invention. Therefore, according to another aspect of the present invention, ortho-substituted bis-aromatic carboxylic acid anhydrides are provided having the structure of Formula II:



20

wherein Ar and R, and the preferred species thereof, are the same as described above with respect to Formula I and R is substituted on each Ar ortho to the anhydride group.

25

The present invention also includes ortho-substituted bis-aromatic dicarboxylic acids, which are novel and non-obvious intermediate compounds having utility in the preparation of ortho-substituted bis-aromatic carboxylic acid anhydrides. Therefore, according to another aspect of the present invention, an ortho-substituted bis-aromatic dicarboxylic acid is provided having the structure of HOOC-Ar-R-Ar-COOH, wherein Ar and R, and the preferred species thereof, are the same as described above with respect to Formula I, and R is substituted on each Ar ortho to each carboxylic acid group.

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The aromatic polyanhydrides of the present invention meet

the need for moldable biocompatible biodegradable polymers. Therefore, the present invention also includes implantable medical devices containing the aromatic polyanhydrides of the present invention. When Ar and R are selected so that the aromatic polyanhydride hydrolyzes to form therapeutic salicylates, the aromatic polyanhydrides have potential uses as biocompatible, biodegradable scaffolding implants for tissue reconstruction in which the degradation products have anti-thrombogenic qualities.

In addition, the aromatic polyanhydrides that hydrolyze to form therapeutic salicylates have potential uses as anti-inflammatory dosage forms, including dosage forms for oral administration, particularly in the treatment of digestive disorders, including bowel disorders such as inflammatory bowel disease, Crohn's disease, and the like. Ar and R may also be selected so that the aromatic polyanhydrides hydrolyze to form therapeutic non-steroidal anti-inflammatory naphthyl and phenyl propionates that resemble compounds such as ibuprofen, ketoprofen, naproxen, and the like, and other aromatic anti-inflammatory compounds such as indomethacin, indoprofen, and the like.

Therefore, the present invention also includes a method for treating inflammation by administering to a patient in need thereof a quantity of the aromatic polyanhydride of the present invention in which Ar and R are selected so that aromatic polyanhydride hydrolyzes to form therapeutic salicylates at the site of inflammation in an amount effective to relieve the inflammation. The aromatic polyanhydrides may be administered orally. This is particularly useful in the treatment of digestive inflammation, such as inflammatory bowel disease, because the therapeutic salicylates are formed in the gastro-intestinal tract of the patient. Methods for treating inflammation with aromatic polyanhydrides that hydrolyze to form therapeutic naphthyl or phenyl propionates are included in the present invention as well, as well as methods for treating inflammation

with aromatic polyanhydrides that hydrolyze to form indomethacin or indoprofen.

The present invention therefore also includes anti-inflammatory oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention that hydrolyze to form therapeutic salicyclates or naphthyl or phenyl propionates, or indomethacin or indoprofen, and a pharmaceutically acceptable excipient. The oral dosage forms may further include a biologically or pharmaceutically active compound to be co-administered with the therapeutic degradation products.

Ar and R may also be selected so that the aromatic polyanhydrides hydrolyzes to form therapeutic antiulcerative drugs such as rosaprostol, therapeutic antifibrotic aminobenzoates and therapeutic vasoconstricting phenylethanolamines and vasoconstricting drugs such as midodrine. Therefore, the present invention also includes a method for therapeutic treatment by administering to a patient in need thereof a quantity of the aromatic polyanhydride of the present invention in which Ar and R are selected so that aromatic polyanhydride hydrolyzes to form rosaprostol, antifibrotic aminobenzoates, vasoconstricting phenylethanolamines and midodrine. The present invention also includes oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention in which Ar and R are selected so that the aromatic polyanhydrides hydrolyze to form rosaprostol, antifibrotic aminobenzoates, vasoconstricting phenylethanolamines and midodrine.

In another embodiment of the present invention, the aromatic polyanhydrides are combined with a quantity of biologically or pharmaceutically active compound sufficient for effective site-specific or systemic drug delivery as described by Gutkowsky et al., J. Biomater. Res., 29, 811-21 (1995) and Hoffman, J. Controlled Release, 6, 297-305 (1987). The biologically or pharmaceutically active compound may be physically admixed, embedded or dispersed in the polymer

matrix. Alternatively, derivatives of biologically and pharmaceutically active compounds can be attached to repeating units of the polymers of the present invention by covalent bonds linked to an Ar ring or an R organic moiety. This
5 provides for sustained release of the biologically or pharmaceutically active compound.

Another aspect of the present invention provides a method for site-specific or systemic drug delivery by implanting in the body of a patient in need thereof an implantable drug
10 delivery device containing a therapeutically effective amount of a biologically or pharmaceutically active compound in combination with an aromatic polyanhydride of the present invention.

A more complete appreciation of the invention and many
15 more other intended advantages can be readily obtained by reference to the following detailed description of the preferred embodiments and claims, which disclose the principles of the invention and the best modes which are presently contemplated for carrying them out.
20

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides aromatic polyanhydrides with improved degradation properties and processability having repeating units with the structure of Formula I in which Ar and R are the same as described above with respect to Formula I. R preferably has a structure of $-Z_1-R_1-Z_1-$, in which R_1 is a difunctional organic moiety and both Z_1 's are difunctional moieties independently selected from ethers, esters, amides, anhydrides, urethanes, carbamates, carbonates, sulfides, and the like. R_1 may be an alkylene group containing from 1 to 20, and preferably 6, carbon atoms, or R_1 may be a group having from 2 to 30, and preferably 6, carbon atoms having a structure selected from $(-\text{CH}_2-\text{CH}_2-\text{O}-)_n$, $(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-)_n$, and $(-\text{CH}_2-\text{CHCH}_3-\text{O}-)_n$, or R_1 may have the structure $-R_2-Z_2-R_3-$,
25 wherein R_2 and R_3 are independently alkylene groups containing
30
35

from 1 to 19 carbon atoms or groups having from 2 to 18 carbon atoms having a structure selected from $(-\text{CH}_2\text{-CH}_2\text{-O-})_n$, $(-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-})_m$, and $(-\text{CH}_2\text{-CHCH}_3\text{-O-})_n$, and Z_2 is selected from the difunctional moieties described above with respect to Z_1 .

5 Ar may be an alkylaryl group, in which a difunctional organic moiety is positioned between each anhydride carbonyl group and the corresponding aromatic ring. Preferably, however, each carbonyl group is directly substituted on the corresponding aromatic ring.

10 Preferred polymers of the present invention have repeating units with the structure of Formula I in which Ar is a phenyl ring and R is selected from $-Z_1\text{-}(-\text{CH}_2\text{-})_n\text{-}Z_1\text{-}$, $-Z(-\text{CH}_2\text{-CH}_2\text{-O-})_m\text{-}Z_1\text{-}$, $-Z(-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-})_m\text{-}Z_1\text{-}$, and $-Z(-\text{CH}_2\text{-CHCH}_3\text{-O-})_n\text{-}Z_1\text{-}$, wherein Z_1 is an ether, ester or amide group and n is from 1 to 20 inclusive, and preferably is 6, and m is selected so that R has from 2 to 20, and preferably 6, carbon atoms.

15 The aromatic polyanhydrides of the present invention may be prepared by the method described in Conix, Macromol. Synth., 2, 95-99 (1996), in which dicarboxylic acids are acetylated in an excess of acetic anhydride at reflux temperatures followed by melt condensation of the resulting carboxylic acid anhydride at 180°C for 2-3 hours. The resulting polymers are isolated by precipitation into diethyl ether from methylene chloride. The described process is essentially the conventional method for polymerizing bis-aromatic dicarboxylic acid anhydrides into aromatic polyanhydrides.

20 Aromatic polyanhydrides in accordance with the present invention have weight average molecular weights of at least about 1500 daltons, up to about 35,000 daltons, calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene standards.

25 The aromatic polyanhydrides of the present invention are produced from orth-substituted bis-aromatic carboxylic acid anhydrides having the structure of Formula II in which Ar, R

and the preferred species thereof are the same as described above with respect to Formula I. As noted above, ortho-substituted bis-aromatic carboxylic acid anhydrides are prepared by acetylation of the corresponding ortho-substituted bis-aromatic carboxylic acids in an excess of acetic anhydride at reflux temperatures. The dicarboxylic acids have the structure of Formula III, wherein Ar, R and the preferred species thereof are the same as described above with respect to Formula I.

The dicarboxylic acids are prepared by reacting a stoichiometric ratio of aromatic carboxylic acid having the structure $Z_2\text{-Ar-COOH}$ and a compound having a structure $Z_4\text{-R-Z}_2$, wherein Ar is a substituted or unsubstituted aromatic ring on which Z_2 is substituted ortho to the carboxylic acid group, R is a difunctional organic moiety and Z_2 and Z_4 are functional groups selected to provide the linkage desired between the difunctional organic moiety and the two aromatic rings.

Suitable Z_2 and Z_4 functional groups, and the manner in which they may be reacted to produce the bis-aromatic dicarboxylic acids of the present invention, may be readily determined by those of ordinary skill in the art without undue experimentation. For example, for aromatic polyanhydrides having the structure of Formula I in which Ar is a phenyl group and R is $-O\text{-(CH}_2\text{-)}_5\text{-O-}$, the ortho-substituted bis-aromatic dicarboxylic acid starting material may be prepared by reacting o-salicylic acid with 1,6-dibromohexane.

The aromatic polyanhydrides of the present invention can be isolated by known methods commonly employed in the field of synthetic polymers to produce a variety of useful articles with valuable physical and chemical properties. The new polymers can be readily processed by solvent casting to yield films, coatings, dishes and sponges with different geometric shapes for design of various medical implants, and may also be processed by compression molding and extrusion. Medical implant applications include the use of aromatic polyanhydrides to form shaped articles such as vascular grafts

and stents, bone plates, sutures, implantable sensors, implantable drug delivery devices, stents for tissue regeneration, and other articles that decompose harmlessly within a known time period.

5 The polymers of the present invention include aromatic polyanhydrides having a repeating unit with the structure of Formula I in which Ar and R are selected to provide aromatic polyanhydrides that hydrolyze to form therapeutically useful salicylates. As noted above, the salicylates may be
10 employed to treat inflammation, particularly digestive inflammation such as inflammatory bowel disorders. Thus, implantable or ingestible drug delivery devices of the present invention include oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention that
15 hydrolyze to form therapeutic salicylates, in combination with a pharmaceutically acceptable excipient. The oral dosage forms function to deliver salicylates to the site of inflammation, either directly, or by being absorbed into the bloodstream from the digestive tract. The salicylates may be
20 supplemented with other therapeutic agents in the polymer matrix.

Examples of the therapeutic salicylates include, but are not limited to, thymotic acid, 4,4-sulfinyldiniline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid, acetylsalicylic acid, and the like. The identification of Ar and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutically useful salicylates can be readily determined by those of ordinary skill in the art without undue experimentation.

35 Ar and R may also be selected so that the aromatic polyanhydrides hydrolyze to form therapeutic non-steroidal anti-inflammatory phenyl and naphthyl propionates,

indomethacin and indoprofen. The identification of Ar and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutic anti-inflammatory compounds can also be readily determined by those of ordinary skill in the art without undue experimentation.

Ar and R may also be selected so that the aromatic polyanhydrides hydrolyze to form other therapeutic compounds. For example, Ar and R may be selected to provide an aromatic polyanhydride that hydrolyzes to form the antiulcerative drug rosaprostol. Ar and R may also be selected to provide aromatic polyanhydrides that hydrolyze to form antifibrotic aminobenzoates. Ar and R may further be selected to provide polyanhydrides that hydrolyze to form the vasoconstricting drug midodrine, as well as vasoconstricting phenylethanolamines. Again, the identification of Ar and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutic compounds can readily be determined by those of ordinary skill in the art without undue experimentation.

Pharmaceutically acceptable excipients for oral administration are well known and include diluents such as lactose, sucrose, mannitol, sorbitol, cellulose, glycine, and the like, lubricants such as silica, talc, stearic acid and salts thereof, and the like, binders such as magnesium aluminum silicate, starches such as corn starch, methyl cellulose, and the like, and disintegrating agents such as starches, agar, and the like, as well as dyestuffs, flavors and sweeteners. The dosage forms are manufactured in a manner that is in itself well known, for example, by means of conventional mixing, granulating or dragee-making processes.

The quantity of aromatic polyanhydride that hydrolyzes to form an amount of therapeutic salicylate effective to relieve inflammation can be readily determined by those of ordinary skill in the art without undue experimentation. The quantity essentially corresponds stoichiometrically to the amount of salicylate known to produce an effective treatment. Oral

dosage forms of aromatic polyanhydrides that hydrolyze to form other therapeutic non-steroidal anti-inflammatory compounds and other therapeutic compounds are prepared and administered in a similar manner.

5 The ortho-substituted aromatic polyanhydrides of the present invention exhibit desirable adhesion to cell cultures. The disruption of crystallinity is believed to improve the attachment and growth of cells and may facilitate specific interactions with proteins, peptides and cells. The aromatic 10 polyanhydrides of the present invention are thus useful as scaffolding implants for tissue reconstruction. The polymer surfaces may also be modified by simple chemical protocols to attach specific peptides or to immobilize proteins to elicit 15 selective cellular responses in tissue engineering applications or in implant design.

Controlled drug delivery systems may also be prepared, in which a biologically or pharmaceutically active agent is physically embedded or dispersed into the polymeric matrix, physically admixed with, or covalently bonded to the aromatic 20 polyanhydride. Covalent bonding is accomplished by providing an aromatic polyanhydride having reactive functional groups on one or more Ar groups or R moieties and reacting the polyanhydride with a derivatized or underivatized biologically or pharmaceutically active compound capable of reacting with 25 the functional group on the aromatic polyanhydride to form a covalent bond. Thus, biologically or pharmaceutically active compounds may be linked to aromatic polyanhydrides by means of ester groups, amide groups, and the like.

30 Examples of biologically or pharmaceutically active compounds suitable for the use in the present invention include acyclovir, cephradrine, malphalan, procaine, ephedrine, adriamicin, daunomycin, plumbagin, atropine, quinine, digoxin, quinidine, biologically active peptides, chlorin e₆, cephadrine, cephalothin, penicillin IV, nicotinic acid, chemodeoxycholic acid, chlorambucil, and the like. 35 Biologically active compounds, for the purposes of the present

invention, are additionally defined as including cell mediators, biologically active ligands, and the like. The compounds are covalently bonded to the aromatic polyanhydride by methods well understood by those of ordinary skill in the art. Drug delivery compounds may also be formed by physically blending the biologically or pharmaceutically active compound to be delivered with the aromatic polyanhydrides of the present invention using conventional techniques well-known to those of ordinary skill in the art.

The following non-limiting examples set forth hereinbelow illustrate certain aspects of the invention. All parts and percentages are by weight unless otherwise noted and all temperatures are in degrees Celsius. Except for acetic anhydride and ethyl ether (Fisher Scientific), all solvents and reagents were obtained from Aldrich Chemical. All solvents were HPLC grade. All other reagents were of analytical grade and were purified by distillation or recrystallization.

All compounds were characterized by a proton nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, gel permeation chromatography (GPC), high performance liquid chromatography (HPLC), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA). Infrared spectroscopy was performed on an AT1 Mattson Genesis (M100) FTIR Spectrophotometer. Samples were prepared by solvent casting on NaCl plates. ^1H and ^{13}C NMR spectroscopy was obtained on a Varian 200 MHz or Varian 400 MHz spectrometer in solutions of CDCl_3 or DMSO-d_6 with solvent as the internal reference.

GPC was performed on a Perkin-Elmer Advanced LC Sample Processor (ISS 200) with PE Series 200 LC Pump and a PE Series LC Refractive Index Detector to determine molecular weight and polydispersity. The data analysis was carried out using Turbochrom 4 software on a DEC Celebris 466 computer. Samples were dissolved in tetrahydrofuran and eluted through a mixed bed column (PE PL gel, 5 μm mixed bed) at a flow rate of 0.5

mL/min. Samples (about 5 mg/mL) were dissolved into the tetrahydrofuran and filtered using 0.5 µm PTFE syringe filters prior to column injection. Molecular weights were determined relative to narrow molecular weight polystyrene standards (Polysciences, Inc.).

Thermal analysis was performed on a Perkin-Elmer system consisting of a TGA 7 thermal gravimetric analyzer equipped with PE AD-4 autobalance and Pyris 1 DSC analyzer. Pyris software was used to carry out data analysis on a DEC Venturis 5100 computer. For DSC, an average sample weight of 5-10 mg was heated at 10°C/min. at a 30 psi flow of N₂. For TGA, an average sample weight of 10 mg was heated at 20C°/min under a 8 psi flow of N₂. Sessile drop contact angle measurements were obtained with an NRL Goniometer (Rame-hart) using distilled water. Solutions of polymer in methylene chloride (10% wt/vol.) were spun-coated onto glass slips, at 5,000 rpm for 30 seconds.

EXAMPLES

Example I-Preparation of 1,6-Bis(o-Carboxyphenoxy) Hexane Dicarboxylic Acid
To a mixture of salicylic acid (77.12 g, 0.5580 mole) and distilled water (84mL) sodium hydroxide (44.71 g, 1.120 mole) was added. The reaction was brought to reflux temperature before 1,6-dibromohexane (45.21 g, 0.2790 mole) was added drop-wise. Reflux was continued for 23 hours after which additional sodium hydroxide (11.17 g, 0.2790 mole) was added. The mixture was refluxed for 16 more hours, cooled, filtered, and washed with methanol. The yield was 48.8%.

Example II-Preparation of 1,6-Bis(o-Carboxyphenoxy) Hexane Monomer (o-CPH)

The dicarboxylic acid of Example I was acetylated in an excess of acidic anhydride at reflux temperature. The resulting monomer was precipitated from methylene chloride

into an excess of diethyl ether. The yield was 66.8%.

Example III-Preparation of Poly(1,6-Bis(o-Carboxyphenoxy) Hexane) (Poly(o-CPH))

5 The monomer of Example II was polymerized in a melt condensation performed at 180°C for 3 hours under vacuum in a reaction vessel with a side arm. The polymerization vessel was flushed with nitrogen at frequent intervals. The polymer was isolated by precipitation into diethyl ether from
10 methylene chloride. The yield was quantitative.

15 All compounds were characterized by nuclear magnetic resonance spectroscopy, GPC, differential scanning calorimetry (DSC), thermal gravimetric analysis, contact angle measurements, UV spectroscopy, mass spectroscopy, elemental analysis and high pressure liquid chromatography (HPLC).

20 The o-CPH monomer was polymerized by melt polycondensation for 60 minutes at temperatures ranging from 100° to 300°C. Analysis of the resulting polymers by GPC indicated that the highest molecular weight, coupled with the lowest polydispersity index occurred at 260°C.

25 The poly(o-CPH) was generally soluble in methylene chloride and chloroform, while the poly(p-CPH) was not. The poly(o-CPH) was slightly soluble in tetrahydrofuran, acetone and ethyl acetate.

30 Disks of poly(o-CPH), poly(p-CPH) and, as a reference, poly(lactic acid glycolic acid) were prepared and placed in 0.1 phosphate buffer solution at 37°C for 4 weeks. The degradation media was replaced periodically. The degradation profile was linear up to three weeks time.

35 In currently used polyanhydride systems, the aromatic groups are para-substituted. This substitution pattern results in higher melt and glass transition temperatures and decreased solubility, thus ultimately making these para-substituted polymers difficult to process.

40 Poly(o-CPH), unlike poly(p-CPH), has both a lower melting point (65°C vs. 143°C) and glass transition temperature (35°C

vs. 47°C). It is also possible to solution cast poly(o-CPH) using low-boiling solvents whereas poly(p-CPH) is relatively insoluble in most organic and aqueous solvents. This structural modification gives a polymer whose hydrolysis products are chemically similar to aspirin. Aspirin is an anti-inflammatory agent derived from salicylic acid, which is one of the reagents used to synthesize the inventive polyanhydrides. Therefore, the degradation products of this polymer may actually aid in patient recovery. Because of pliability and ease of processing, the aromatic polyanhydrides of the present invention have great potential as polymer scaffolds for wound healing.

15 **Example IV-Preparation of 1,3-bis(o-carboxyphenoxy)propane dicarboxylic acid**

1,3-dibromopropane (14.7 mL, 0.145 mole) was added to a mixture of salicylic acid (40.0 g, 0.290 mole), distilled water (44 mL) and sodium hydroxide (23.2 g, 0.580 mole) using the method described in Example I. After 4 hours, additional sodium hydroxide (5.79 g, 0.145 mole) was added to the reaction mixture. Reflux was continued for another 4 hours, after which the mixture was cooled, filtered and washed using the methods described in Example I. The yield was 37.7%

25 **Example V-Preparation of
poly(1,3-bis(o-carboxyphenoxy)propane)**

30 The dicarboxylic acid of Example IV was acetylated using the methods of Example II. The acetylated dicarboxylic acid was then polymerized using the methods described in Example III. The resulting polymer had a M_w of 8,500 daltons and a polydispersity of 2.3.

35 Contact angle measurements on solvent-cast films demonstrated that the hexyl chain of the polymer of Example III increased the surface hydrophobicity relative to the shorter propyl chain of the polymer of Example V. A comparison of thermal characteristics emphasized the effects

of lengthening the alkyl chain. In particular, the polymer of Example III has a T_g of 34°C and a T_d of 410°C, while the polymer of Example V had a T_g of 50°C and a T_d of 344°C. Thus, the hexyl chain decreased the glass transition temperature (T_g) relative to the propyl chain, reflecting the increased flexibility of the polymer chain. The opposite trend was observed for decomposition temperatures (T_d), with the longer alkyl chain increasing the T_d .

Optimum polycondensation conditions were determined for the polymer of Example III. Optimum conditions were defined as those that yielded a crude polymer with the highest molecular weight and highest T_g . Higher reaction temperatures decreased the M_w values (measured by GPC) with a concurrent increase in polydispersity. As expected for a condensation polymerization, longer reaction times yielded polymers with higher molecular weights. However, over longer reaction times, there appeared a subsequent decrease in T_g . Based on these results, the optimum conditions were defined as temperatures of 220°C for 150 minutes under a vacuum.

Example VI-Preparation of 1,8-bis[ω -(benzylcarboxy)carboxy phenyl] octane dicarboxylic acid ester

The initial synthesis of poly(anhydride-ester) dicarboxylic acid monomers was attempted using the same methodology used for the poly(anhydride-ether) dicarboxylic monomers of Example III. It was found, however, that the reactivity of the phenol was enhanced by benzylation of the carboxylic acid group. In addition, the solubility of benzyl salicylate in organic media increased the ability of the reaction to move forward.

Thus, benzyl salicylate (1.530 g, 6.720 mmole) and distilled tetrahydrofuran were combined under an inert atmosphere in a reaction flask. An ice-salt bath was placed under the reaction flask and the addition of 60% sodium hydride (0.4840 g, 12.10 mmole) followed. After one hour, sebacoyl chloride (0.7850 g, 3.280 mmole) was added drop-wise

to the 0°C reaction mixture. After 30 minutes, the reaction mixture was vacuum filtered, the filtrate collected and the solvent removed to reveal to yield the free carboxylate as a white solid residue. Purification was performed using a chromatron with ethyl acetate/methylene chloride (20/80) as the solvent system. The yield was 43%.

5
Example VII-Polymerization of Poly(1,8-bis(o-dicarboxyphenyl)octane)

10 To remove the benzyl protecting groups, the 1,8-bis[(benzylcarboxy)carboxyphenyl]octane dicarboxylic acid ester of Example VI (0.06000 g, 0.9620 mmole) was dissolved in methylene chloride in a reaction flask (60.00 mL). The catalyst Pd-C (10%, 1.200 g) was added to the reaction flask. 15 After 30 minutes, the reaction was complete. The reaction mixture was filtered and the solvent removed to yield the free dicarboxylic acid as a white solid residue which was recrystallized using petroleum ether and methylene chloride. The yield was 45%.

20 The dicarboxylic acid was acetylated using the methods described in Example II and the acetylated dicarboxylic acid was then polymerized using the methods described in Example III. The resulting polymer had a M_w of 3,000 daltons and a polydispersity of 1.40.

25 Subsequent polymerizations yielded polymers with M_w 's ranging from 2,000 to 5,000 daltons with corresponding polydispersities of approximately 1.40.

30 The poly(anhydride esters) of Example VII were compression molded into circular discs and placed in phosphate buffered saline solution under acidic, neutral and basic conditions. Over the course of a three-week degradation study, the polymers in the acidic and neutral solutions showed no observable changes, whereas the polymer in the basic media showed significant morphological changes over time.

35

Example VIII-Preparation of Poly[(1,8-bis(o-dicarboxyphenyl) octane)-(1,6-bis(p-carboxyphenoxy) hexane] copolymers

The 1,8-bis(o-dicarboxyphenyl) octane of Example II was copolymerized with 1,6-bis(p-carboxyphenoxy) hexane using the methods described in Example III. In an in vivo mouse study, each mouse was implanted with 2 polymers, the copolymer of Example VIII and poly(1,6-bis(p-carboxyphenoxy)hexane). Each polymer was compression molded for 1 to 5 minutes at 1 to 20 K psi depending on the thickness of polymer needed. The polymer was placed under the palatal gingival mucosa adjacent to the first maxillary molars. The mice were sacrificed at 1, 4 and 10 day intervals and demonstrated the biocompatibility and biodegradability in vivo of the polymers of the present invention, with salicylic acid being released upon degradation, via hydrolysis of the polymer backbone.

STATEMENT OF INDUSTRIAL APPLICABILITY

The polymers of the present invention have a variety of pharmaceutical applications, particularly as anti-inflammatory compounds.

The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as defined by the claims. As would be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the spirit and the scope of the invention, and all such variations are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An aromatic polyanhydride comprising a repeating
5 unit having the structure:



10 wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group.

15 2. The aromatic polyanhydride of claim 1, wherein Ar is a phenyl group and R is $-Z_1-R_1-Z_1-$, wherein R_1 is a difunctional organic moiety and Z_1 is a difunctional moiety selected from the group consisting of ethers, ester, amides, urethanes, carbamates and carbonates.

20 3. The aromatic polyanhydride of claim 2, wherein Z_1 is an ether, ester or amide group, and R_1 is selected from the group consisting of $(-\text{CH}_2-)_n$, $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-)_n$, and $(-\text{CH}_2-\text{CHCH}_3-\text{O}-)_m$, wherein n is from 1 to 20, inclusive and m is selected so that R_1 has between 2 and 20 carbon atoms, inclusive.

25 4. The aromatic polyanhydride of claim 3, wherein n is 6.

30 5. The aromatic polyanhydride of claim 2, wherein R_1 is $-\text{R}_2-Z_2-\text{R}_3-$, wherein R_2 and R_3 are difunctional organic moieties and Z_2 is a difunctional moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

6. The aromatic polyanhydride of claim 5, wherein R₂ and R₃ are independently selected from the group consisting of alkylene groups containing from 1 to 19 carbon atoms, (-CH₂-CH₂-O-)_m, (-CH₂-CH₂-CH₂-O-)_m, and (-CH₂-CHCH₃-O-)_m, wherein 5 m is between 2 and 18, inclusive.

7. The aromatic polyanhydride of claim 1, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates, non-steroidal anti-inflammatory naphthyl or phenyl propionates, indomethacin, indoprofen, rosaprostal, antifibrotic aminobenzoates, midodrine, or vasoconstricting phenylethanolamimes. 10

8. The aromatic polyanhydride of claim 7, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group consisting of thymotic acid, 4,4-sulfinyldinailine, 4-sulfanilamidosalicylic acid, sulfanilic acid, 20 sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid and acetylsalicylic acid. 25

9. The aromatic polyanhydride of claim 7, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group 30 consisting of ibuprofen, ketoprofen and naproxin.

10. An implantable medical device comprising the aromatic polyanhydride of claim 1.

11. The implantable medical device of claim 10, wherein said device is a scaffolding implant for tissue reconstruction.

5 12. The implantable medical device of claim 10 comprising a biologically or pharmaceutically active compound in combination with said aromatic polyanhydride, wherein said active compound is present in amounts sufficient for therapeutically effective site-specific or systemic drug delivery.

10 13. The implantable medical device of claim 12, wherein said biologically or pharmaceutically active compound is covalently bonded to said aromatic polyanhydride.

15 14. A method for site-specific or systemic drug delivery comprising implanting in the body of a patient in need thereof an implantable drug delivery device comprising a therapeutically effective amount of a biologically or pharmaceutically active compound in combination with the aromatic polyanhydride of claim 1.

20 15. The method of claim 14, wherein said biologically or pharmaceutically active compound is covalently bonded to said aromatic polyanhydride.

25 16. A drug delivery system comprising the aromatic polyanhydride of claim 1 physically admixed with a biologically or pharmaceutically active agent.

30 17. A drug delivery system comprising a biologically or pharmaceutically active agent physically embedded or dispersed into a polymeric matrix formed from the aromatic polyanhydride of claim 1.

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18. A drug delivery system comprising a biologically or pharmaceutically active agent covalently bonded to the aromatic polyanhydride of claim 1.

5 19. An ortho-substituted bis-aromatic dicarboxylic acid anhydride having the structure:



10 wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group.

15 20. The acid anhydride of claim 19, wherein Ar is a phenyl group and R is $-Z_1-R_1-Z_2-$, wherein R_1 is a difunctional organic moiety and Z_1 is a difunctional moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

20 21. The acid anhydride of claim 20, wherein Z_1 is an ether, ester or amide group; and R_1 is selected from the group consisting of $(-\text{CH}_2)_n$, $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-)_m$ and $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-)_m$, wherein n is from 1 to 20, inclusive, and m is selected so that R_1 has between 2 and 20 carbon atoms, inclusive.

25 22. The acid anhydride of claim 21, wherein n is 6.

30 23. An ortho-substituted bis-aromatic dicarboxylic acid having the structure HOOC-Ar-R-Ar-COOH , wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety on both Ar rings ortho to each carboxylic acid group.

35 24. The dicarboxylic acid of claim 23, wherein Ar is a phenyl group and R is $-Z_1-R_1-Z_2-$, wherein R_1 is a difunctional

organic moiety and Z_1 is a difunctional organic moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

5 25. The dicarboxylic acid of claim 24, wherein Z_1 is an ether, ester or amide group, and R_1 is selected from the group consisting of $(-\text{CH}_2)_n$, $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-)_n$ and $(-\text{CH}_2-\text{CHCH}_2-\text{O}-)_p$, wherein n is from 1 to 20, inclusive, and m is selected so that R_1 has between 2 and 20 carbon atoms,
10 inclusive.

26. The dicarboxylic acid of claim 25, wherein n is 6.

15 27. A method for treating inflammation comprising administering to a patient in need thereof a quantity of the aromatic polyanhydride of claim 1, Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates, phenyl or naphthyl propionic acids, indomethacin or indoprofen at the site of said inflammation in
20 an amount effective to relieve said inflammation.

25 28. The method of claim 27, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group consisting of thymotic acid, 4,4-sulfinyldiniline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid and acetylsalicylic acid.
30

29. The method of claim 27, wherein Ar and z are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group consisting of
5 ibuprofen, ketoprofen and naproxin.

30. The method of claim 27, wherein said aromatic polyanhydride is administered orally.

10 31. A therapeutic method comprising administering to a patient in need thereof an effective amount of an aromatic polyanhydride according to claim 1, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form rosaprostol, antifibrotic aminobenzoates, midodrine or
15 vasoconstricting phenylethanolamines.

32. The method of claim 31, wherein said aromatic polyanhydride is administered orally.

20 33. An anti-inflammatory oral dosage form consisting essentially of an effective amount of the aromatic polyanhydride of claim 1, and a pharmaceutically acceptable excipient, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates, phenyl or naphthyl propionic acids, indomethecin, or
25 indoprofen.

30 34. The oral dosage form of claim 33, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group consisting of thymotic acid, 4,4-sulfinyldinainiline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone,
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salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid and acetylsalicylic acid.

5

35. The oral dosage form of claim 33, wherein Ar and Z are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group consisting of
10 ibuprofen, ketoprofen and naproxin.

36. The oral dosage form of claim 33, further comprising a second therapeutic agent to be administered in combination with said polyanhydride.

15

37. A method for treating digestive inflammation comprising orally administering to a patient in need thereof a quantity of the aromatic polyanhydride of claim 1, wherein Ar and R are selected so that said aromatic polyanhydride
20 hydrolyzes to form therapeutic salicylates at the site of said inflammation in an amount effective to relieve said inflammation.

38. The method of claim 37, wherein said therapeutic salicylate is selected from the group consisting of thymotic acid, 4,4-sulfinyldiniline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid and acetylsalicylic acid.

39. A therapeutic treatment method comprising administering to a patient in need thereof an effective quantity of an aromatic polyanhydride according to claim 1,
35 wherein Ar and R are selected so that said aromatic

polyanhydride hydrolyzes to form rosaprostan, antifibrotic aminobenzoates, midodrine, or vasoconstricting phenylethanamines.

- 5 40. The method of claim 39, wherein said aromatic polyanhydride is administered orally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18816**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :C08G 63/00, 63/02, 67/00, 69/00

US CL : 528/176, 193, 271, 272

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 528/176, 193, 271, 272

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,264,540 A (COOPER ET AL.) 23 November 1993 (23-11-93), abstract, column 5 lines 5-55, column 6 lines 5-55	1-40
X	US 4,997,904 A (DOMB) 05 March 1991 (05-03-91), abstract, column 2 Lines 5-55, column 4 Line 5-30.	1-40

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

14 DECEMBER 1998

Date of mailing of the international search report

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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

TERRESSA MOSLEY

Telephone No. (703) 308-0651